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Review

# Treatment outcomes of human bartonellosis: a systematic review and meta-analysis

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SUMMARY

*Background:* *Bartonella henselae*, *Bartonella quintana*, and *Bartonella bacilliformis* are responsible for the majority of cases of bartonellosis in humans. These species have various unique epidemiologic characteristics, clinical manifestations, and treatment approaches. The objective of this study was to summarize the evidence on the treatment for the three most common species of Bartonella in humans.
*Methods:* We searched electronic databases through August 2011 for randomized controlled trials and observational studies designed to evaluate the efficacy and safety of the regimens used to treat diseases produced by *B. henselae*, *B. quintana*, and *B. bacilliformis*. Study selection and appraisal were done in duplicate.
*Results:* We found two randomized and seven non-randomized studies at high risk of bias. For cat scratch disease, antibiotics did not significantly affect the cure rate or time to achieve cure. In chronic bacteremia, gentamicin and doxycycline significantly increased the resolution rate. The recommended treatment was not better than other regimens for infectious endocarditis and bacillary angiomatosis.
*Conclusions:* Current clinical practice for the treatment of bartonellosis relies mostly on expert opinion and antimicrobial susceptibility data. Randomized controlled trials are needed in the field to compare different treatment options.
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## 1. Introduction

Three species of Bartonella are responsible for the vast majority of infections in humans: *B. henselae*, *B. quintana*, and *B. bacilliformis*. Each one of these species leads to different clinical manifestations and requires different treatment approaches.[1,2] While the infection caused by *B. henselae* has a worldwide distribution,[3] with an incidence of 3.7 per 100 000 (according to a study from the USA),[4] *B. quintana* and *B. bacilliformis* cases are geographically and demographically limited. *B. quintana* has predominantly involved homeless persons with head or body lice exposure in Europe and the USA.[5] Its incidence is unclear, as only a small portion of the infected population will develop overt clinical disease.[5,6] On the other hand, *B. bacilliformis* is restricted to certain mountain regions of Peru, Ecuador, and Colombia, known as the 'verruge zone',[7] having an incidence in the general population of 2.7 cases of bartonellosis (either Oroya fever, verruga peruana, or asymptomatic infection) per 100 person-years.[8]

In immunocompetent patients, *B. henselae* can cause an acute infection called cat scratch disease (CSD), which usually manifests as subacute, regional lymphadenopathy. Likewise, infection caused by *B. bacilliformis* can manifest as an acute phase called Oroya fever or as a chronic phase in Oroya fever survivors called verruga peruana. The acute and chronic states of *B. quintana* infection are trench fever and chronic bacteremia, respectively.[9,10]

When the affected patients are immunocompromised subjects, mainly but not limited to HIV patients, Bartonella species can produce a broad array of manifestations, including bacillary

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angiomatosis, peliosis hepatis, splenitis, osteomyelitis, and bacteremia.[11,12]

Bartonella infections present a unique challenge for several reasons, including the high mortality of infected humans who do not receive treatment in the case of *B. bacilliformis* acute infection,[13,14] and the persistence and frequent relapses due to the existence of an intraerythrocytic phase that may provide a protective niche for the bacteria.[15]

Current recommendations for the choice, route, and extent of an antimicrobial treatment for infections caused by *Bartonella spp* are made depending on the infective species, the clinical course, and the immunological state of the patient. They are mainly based on nonsystematic clinical observations and expert panel consensus statements.[16–18] Unfortunately these approaches are limited by deficiencies in the human process of making inferences.[19]

No systematic reviews have been done to summarize and appraise the evidence informing the treatment decisions for infections caused by *Bartonella spp*. We believe that by gathering and analyzing the current evidence concerning the therapeutics of Bartonella infections, we may be able to draw evidence-based conclusions or, in the lack of it, incite future development of evidence-based knowledge concerning this important infection. Therefore, we conducted this systematic review to inform current treatment decisions and future research activities.

## 2. Methods

Search and analysis methods, eligibility criteria, and the outcomes of interest were specified in advance in a protocol developed by the study investigators.

### 2.1. Eligibility criteria

We included randomized controlled trials (RCTs) and observational studies that enrolled patients of any age and gender, designed to evaluate the efficacy and safety of the different regimens used to treat diseases produced by the three most common species of human Bartonella (Table 1).

### 2.2. Search methods

An expert reference librarian (PJE) designed and conducted an electronic search strategy following the protocol (Table 2). We searched electronic databases to identify relevant studies (Ovid Medline, Ovid EMBASE, Ovid Cochrane Library, Web of Science, Scopus, PsycInfo, and CINAHL) from their inception through August 2011. To identify additional candidate studies, we reviewed the reference lists of the eligible primary studies, narrative reviews, and systematic reviews. We also contacted experts on the topic for this purpose and performed a manual search for unpublished studies or studies published in non-indexed journals (1. The Brazilian Journal of Infectious Diseases, 2. Revista Medica Herediana, 3. Diagnóstico, 4. Folia Dermatológica Peruana, 5. Revista del Instituto de Medicina Tropical de Sao Paulo, 6. Acta Medica Peruana, 7. Revista Peruana de Enfermedades Infecciosas y Tropicales, 8. CID (Clinical Infectious Diseases), 9. Revista de Gastroenterología del Perú, 10. Revista de Neuro-Psiquiatría).

**Table 1**
Diseases produced by the most common species of human Bartonella.

| |
|---|
| *Bartonella henselae:* |
| Cat scratch disease (CSD) |
| Bacillary angiomatosis |
| Peliosis hepatis |
| Infectious endocarditis |
| Chronic bacteremia |
| *Bartonella quintana:* |
| Bacillary angiomatosis |
| Trench fever |
| Infectious endocarditis |
| Chronic bacteremia |
| *Bartonella bacilliformis:* |
| Carrion disease |
| Acute phase |
| Chronic phase |

### 2.3. Selection of studies

Two reviewers working independently considered the potential eligibility of each of the abstracts and titles that resulted from executing the search strategy. Eligible studies were reviewed in full text versions (all available versions of each study). There were no disagreements between the reviewers in the full text screening.

### 2.4. Data extraction and management

Using a standardized, piloted, and web-based data extraction form and working in duplicate, we abstracted the following descriptive data from each study: full description of participants enrolled (age, diagnosis criteria, severity), interventions they received (type, frequency, and route), control interventions, monitoring methods for efficacy of the follow-up and adherence to the treatment, measures of outcome (specifically defined as event or measure and time frame for the ascertainment of this outcome), and source of funding. We extracted the outcomes of interest at the longest point of complete follow-up.

### 2.5. Outcomes of interest

After the screening process, we extracted the following outcomes from the included studies: clinical cure or response to therapy, death rate, superimposed infectious disease, time to achieve clinical cure, severe adverse effects (defined as any drug effect that was strong enough to force the patient to stop the treatment, grade 2–4[20]), and relapse rates.

### 2.6. Author contact

When data were not available from the published papers, repeated efforts were made to contact the authors. We decided a priori to e-mail the authors twice, 2 weeks apart, and to use mail when an e-mail address was not available.

### 2.7. Assessment of the risk of bias in included studies

To assess the methodological quality of the included RCTs we used the Cochrane risk of bias assessment tool to evaluate: randomization performance and methods, allocation concealment, baseline imbalances, extent of blinding (patients, caregivers, data collectors, outcome assessors, and data analysts), rate of loss to follow-up, and whether adherence was monitored. For observational studies we used the Newcastle–Ottawa quality assessment tool to evaluate how the groups were selected, the comparability between them, whether there was adequate follow-up, and how the outcomes and exposure were ascertained.

### 2.8. Meta-analysis

For dichotomous outcomes we estimated the odds ratio (OR) and for continuous outcomes we estimated the weighted mean difference (WMD). The $I^2$ statistic was used to measure inconsistency in results across studies not attributable to chance.[21] To pool data across studies, we tested a random effects model and a fixed

**Table 2**
Search strategy

**Ovid**

Database(s): EMBASE 1988 to 2011 week 25; Ovid MEDLINE in-process and other non-indexed citations and Ovid MEDLINE 1948 to present, EBM Reviews – Cochrane Central Register of Controlled Trials 2nd Quarter 2011, EBM Reviews – Cochrane Database of Systematic Reviews 2005 to June 2011

| # | Searches | Results |
|---|---|---|
| 1 | exp Anti-Bacterial Agents/ | 1 841 773 |
| 2 | exp antibiotic agent/ | 587 440 |
| 3 | ((antibiotic* or ''anti-biotic*'' or (antimycobacterial or ''anti-mycobacterial'' or antibacterial or ''anti-bacterial'' or bacteriocidal)) adj (agent or agents)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct] | 370 688 |
| 4 | or/1–3 | 1 845 395 |
| 5 | exp Bartonella Infections/dt [Drug Therapy] | 879 |
| 6 | (((bartonellosis or (bartonella or rochalimaea or bartonellaceae)) adj2 (infection* or bacteremia)) or ''cat scratch fever*'' or ''oroya fever*'' or (carrion* adj disease) or ''verruga peruana'' or ''bacillary angiomatosis'' or ''trench fever'').mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct] | 2817 |
| 7 | 5 or (4 and 6) | 1269 |
| 8 | exp controlled study/ | 3 551 676 |
| 9 | exp evidence based medicine/ | 495 377 |
| 10 | evidence-based.mp. | 166 460 |
| 11 | ((control$ or randomized) adj2 (study or studies or trial or trials)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, ps, rs, nm, ui, tx, ct] | 4 545 775 |
| 12 | meta analysis/ | 83 178 |
| 13 | meta-analys$.mp. | 131 591 |
| 14 | exp ''systematic review''/ | 41 492 |
| 15 | systematic review$.mp. | 91 862 |
| 16 | exp Guideline/or exp Practice Guideline/ | 263 122 |
| 17 | guideline$.ti. | 83 824 |
| 18 | or/8–17 | 5 042 389 |
| 19 | exp Cohort Studies/ | 1 285 714 |
| 20 | exp longitudinal study/ | 854 104 |
| 21 | exp retrospective study/ | 600 779 |
| 22 | exp prospective study/ | 512 155 |
| 23 | exp observational study/ | 20 881 |
| 24 | exp comparative study/ | 2145971 |
| 25 | exp clinical trial/ | 1 442 390 |
| 26 | exp evaluation/ | 1 056 005 |
| 27 | exp validation study/ | 25 379 |
| 28 | ((clinical or evaluation or validation or pilot or comparative or cohort or longitudinal or retrospective or prospective or concurrent or follow-up or observational) adj (study or studies or analysis or analyses or trial or trials)).mp. | 6 276 418 |
| 29 | or/19–28 | 6 882 063 |
| 30 | 7 and (18 or 29) | 199 |
| 31 | from 7 keep 828–1267 | 440 |
| 32 | limit 31 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or validation studies) [Limit not valid in EMBASE, CCTR, CDSR; records were retained] | 13 |
| 33 | from 7 keep 1268–1269 | 2 |
| 34 | 30 or 32 or 33 | 199 |
| 35 | limit 34 to human [Limit not valid in CCTR, CDSR; records were retained] | 181 |
| 36 | limit 35 to humans [Limit not valid in CCTR, CDSR; records were retained] | 181 |
| 37 | limit 36 to (book or book series or editorial or erratum or letter or addresses or autobiography or bibliography or biography or comment or dictionary or directory or interactive tutorial or interview or lectures or legislation or news or newspaper article or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in EMBASE, Ovid MEDLINE, Ovid MEDLINE In-Process, CCTR, CDSR; records were retained] | 9 |
| 38 | 36 not 37 | 172 |
| 39 | remove duplicates from 38 | 148 |

**Scopus**

| | |
|---|---|
| 1 | TITLE-ABS-KEY(bartonellosis or (bartonella w/2 infection*) or (rochalimaea w/2 infection*) or (bartonellaceae w/2 infection*) or (bartonella w/2 bacteremia) or (rochalimaea w/2 bacteremia) or (bartonellaceae w/2 bacteremia) or ''cat scratch fever*'' or ''oroya fever*'' or (carrion* w/1 disease) or ''verruga peruana'' or ''bacillary angiomatosis'' or ''trench fever'') |
| 2 | TITLE-ABS-KEY(antibiotic* or ''anti-biotic*'' or (antimycobacterial w/1 agent) or (''anti-mycobacterial'' w/1 agent) or (antibacterial w/1 agent) or (''anti-bacterial'' w/1 agent) or (bacteriocidal w/1 agent) or (antimycobacterial w/1 agents) or (''anti-mycobacterial'' w/1 agents) or (antibacterial w/1 agents) or (''anti-bacterial'' w/1 agents) or (bacteriocidal w/1 agents)) |
| 3 | 1 and 2 |
| 4 | TITLE-ABS-KEY(''comparative study'' OR ''comparative survey'' OR ''comparative analysis'' OR ''cohort study'' OR ''cohort survey'' OR ''cohort analysis'' OR ''longitudinal study'' OR ''longitudinal survey'' OR ''longitudinal analysis'' OR ''retrospective study'' OR ''retrospective survey'' or ''retrospective analysis'' OR ''prospective study'' OR ''prospective survey'' OR ''prospective analysis'' OR ''concurrent study'' OR ''concurrent survey'' OR ''concurrent analysis'' or ''follow-up study'' OR ''follow-up survey'' OR ''follow-up analysis'' or ''observational study'' OR ''observational survey'' OR ''observational analysis'' OR ''clinical study'' OR ''clinical trial'' or ''evaluation study'' OR ''evaluation survey'' OR ''evaluation analysis'' or ''validation study'' OR ''validation survey'' OR ''validation analysis'') |
| 5 | TITLE-ABS-KEY((evidence W/1 based) OR (meta W/1 analys*) OR (systematic* W/2 review*) OR guideline OR (control* W/2 stud*) OR (control* W/2 trial*) OR (randomized W/2 stud*) OR (randomized W/2 trial*)) |
| 6 | 3 and (4 or 5) |

**Table 2** (*Continued*)

| | |
|---|---|
| **Scopus** | |
| 7 | PMID(0*) OR PMID(1*) OR PMID(2*) OR PMID(3*) OR PMID(4*) OR PMID(5*) OR PMID(6*) OR PMID(7*) OR PMID(8*) OR PMID(9*) |
| 8 | 6 and not 7 |
| 9 | DOCTYPE(le) OR DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh) |
| 10 | 8 and not 9 |
| **LILACS** | |
| 1 | Bartonellosis or bartonellaceae OR rochalimaea OR oroya or Bartonella or Carrion disease or Carrion's disease or Carrions disease or verruga peruana or bacillary angiomatosis or trench fever [Words] |

effect model and presented results for both. The analyses were performed using Comprehensive Meta-Analysis (CMA) version 2.2 (Biostat Inc., Englewood, NJ, USA). Data were insufficient to perform the pre-specified subgroup analysis (based on immunity status, risk of bias, and length of treatment). Evaluation of publication bias was not feasible due to heterogeneity and the small number of included studies.[22]

## 3. Results

### 3.1. Search results and study description

The literature search identified 157 articles, of which nine studies met our eligibility criteria. Two were RCTs; one of them evaluated[24] adult patients with CSD and the other[25] enrolled adult patients with chronic bacteremia caused by *B. quintana*. Seven retrospective cohort studies were included in this review; three of them evaluated CSD[26–28] and the other four evaluated chronic *B. quintana* bacteremia,[29] Carrion's disease,[14] bacillary angiomatosis due to *B. henselae* and *B. quintana*,[30] and infectious endocarditis due to *B. henselae* and *B. quintana*[31] (Figure 1).

This review included 751 patients and their mean age was 29.46 years (range 6 months to 72 years). Most of the studies ($n = 6$) did not report the length of the follow-up. Only one study[30] evaluated immunosuppressed patients (patients with HIV who developed bacillary angiomatosis). Table 3 shows the characteristics of the included trials.

### 3.2. Author contact

We attempted to contact two authors by e-mail[14,29] in order to clarify certain characteristics of their trials. We received one answer.

### 3.3. Risk of bias

Both of the RCTs had adequate randomization methods, but the allocation was not concealed in one of them and it was not

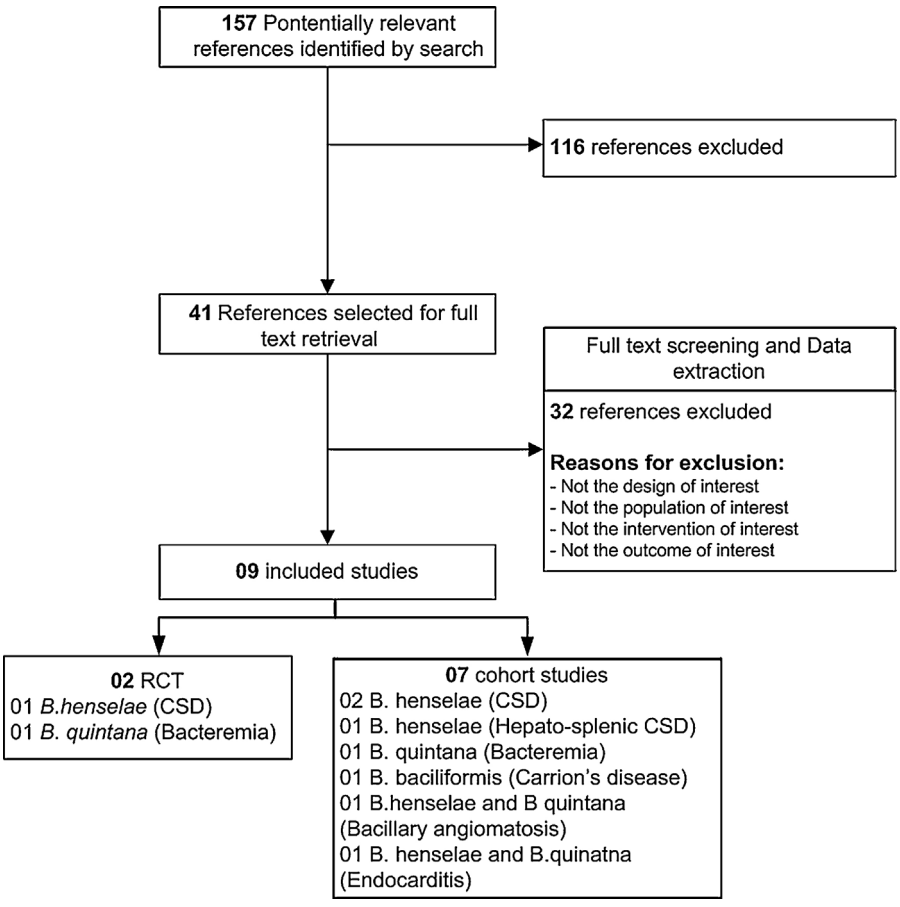


**Figure 1.** Selection process of the included studies.

**Table 3**
Study characteristics

| Study design | *n* | Age, years (mean) | Bacterium/ disease | Patient characteristics, diagnostic criteria, case definition | Follow-up (months) | Intervention and length of the intervention | Control |
|---|---|---|---|---|---|---|---|
| Bass 1998<br>RCT | 35 | 19 | *B. henselae*<br>CSD | Active duty military members and their dependents with laboratory-confirmed, clinically typical CSD<br>Patient with regional lymphadenopathy and a cat scratch/bite or papule distal to the lymph nodes. In patients with regional lymphadenopathy and no skin lesions, a history of intimate contact with a cat that frequently scratched, bit, or licked | Around 2 months: until the initial total lymph node volume has resolved to 20% of that observed at initiation of therapy | Azithromycin<br>5 days | Placebo |
| Foucault 2003<br>RCT | 20 | 54 | *B. quintana*<br>Chronic bacteremia | Patients >18 years old with a positive blood culture for *B. quintana* | 3 months | Gentamicin + doxycycline<br>Mean: 28 days | No treatment |
| Arisoy 1999<br>Retrospective cohort | 19 | 6.9 | *B. henselae*<br>Hepato-splenic CSD | Evidence of hepatic and/or splenic lesions consistent with CSD: ultrasound examination or CT; serological findings consistent with CSD; and serology, cultures, and skin tests negative for other likely causes of the illness | NR: until the onset of clinical abatement of the patient's presenting symptoms and disappearance of fever | Gentamicin, TMP–SMX, rifampin, rifampin + gentamicin, rifampin + TMP–SMX<br>8–17 days | NA |
| Collio 1992<br>Retrospective cohort | 101 | <17 | *B. henselae*<br>CSD | Pediatric patients who were diagnosed with CSD in a pediatric office in Georgia. CSD lymphadenitis, regional lymphadenopathy and adenitis diagnosed according to clinical history | NR: until the problem was solved | TMP–SMX, cephalexin, erythromycin, cloxacillin, amoxicillin and clavulanate, cefaclor<br>7–16 days | No treatment |
| Foucault 2002<br>Retrospective cohort | 42 | NR | *B. quintana*<br>Chronic bacteremia | Homeless people who presented to the emergency departments and those who were admitted to medical facilities in city shelters who had positive blood culture | NR: until 1 week after the last blood culture | β-lactams, doxycycline, doxycycline + rifampin<br>7–28 days | No treatment |
| Margileth 1992<br>Retrospective cohort | 268 | 20 | *B. henselae*<br>CSD | Adult and pediatric patients with CSD who were seen or reported to the authors.<br>Patients had to meet four criteria: (1) history of cat contact and presence of scratch or primary dermal, eye or mucosal contact, (2) positive skin test, (3) negative studies for other causes of lymphadenopathy, (4) characteristic biopsy | NR | Antibiotic therapy (TMP–SMX, ciprofloxacin, gentamicin and rifampin)<br>Mean: 19.6 days | No treatment |
| Maguina 2001<br>Retrospective cohort | 68 | 15 | *B. bacilliformis*<br>Carrion's disease | Peruvian patients, 59% were natives from areas where bartonellosis was endemic and 41% were visitors to such areas — Acute phase: at least one clinical manifestation associated with the acute phase and either a positive blood smear or a positive culture for *B. bacilliformis* (blood or bone marrow) | NR: until the resolution of the disease or death | CAF, CAF + other, ampicillin, norfloxacin<br>10–14 days | No treatment |
| | 77 | 18 | | Eruptive phase: clinical manifestations and characteristic findings on biopsy of one of the lesions | | Streptomycin or rifampin<br>10–14 days | NA |
| Plettenberg 2000<br>Retrospective cohort | 20 | 39 | *B. henselae* and *B. quintana*<br>BA | Patients with HIV who developed bacillary angiomatosis. Typical clinical manifestations and histological findings or identification of the bacteria by molecular biological techniques | NR: until the resolution of the disease or death | Erythromycin, doxycycline, cefuroxime, imipenem<br>NR | NA |
| Raoult 2003<br>Retrospective cohort | 49 | 51 | *B. quintana*<br>IE | Adult patients, mainly men, who were diagnosed with endocarditis. Dukes criteria + positive culture, DNA amplification from valvular tissue or blood, or when patients had IgG titers ≥1/800 | NR | β-lactams, β-lactams + aminoglycosides, rifampin ± other, aminoglycosides ± other, doxycycline ± other non-aminoglycoside, doxycycline ± other, fluoroquinolone ± other<br>NR | NA |
| | 12 | | *B. henselae*<br>IE | | | | |

BA, bacillary angiomatosis; CAF, chloramphenicol; CSD, cat scratch disease; CT, computed tomography; IE, infectious endocarditis; NA, not applicable,; NR, not reported; RCT, randomized controlled trial; TMP–SMX, trimethoprim–sulfamethoxazole.

reported in the other. One was an open label study and the other was double-blinded. Both of them reported an important attrition during follow-up – 17% and 20%.

The overall risk of bias in this body of evidence was considered high, since the RCTs had a high rate of loss to follow-up and no clear allocation concealment and the non-RCTs were retrospective with small sample sizes (the largest sample size was 268 patients). Table 4 describes the quality of the included studies.

### 3.4. Outcomes of interest

#### 3.4.1. Cat scratch disease

We found two studies that evaluated antibiotic therapy in CSD. The first was an RCT comparing azithromycin to placebo, and the second was a non-randomized observational study comparing trimethoprim–sulfamethoxazole (TMP–SMX), ciprofloxacin, gentamicin, and rifampin to no treatment. A meta-analysis of these two studies did not show a statistically significant effect in terms of cure rate (all patients in both arms were cured, 130 patients in two included studies) or time to achieve cure (WMD 1.49 days, 95% CI −9.38 to 12.35, $p = 0.79$, $I^2 = 23\%$) (Figure 2). A third study evaluated 19 patients with a prolonged duration of fever (3 weeks) due to hepatosplenic CSD[26] and found that the patients who received rifampin alone or in combination improved after 1–5 days of treatment, and patients who received other treatments (gentamicin or TMP–SMX) improved after 3–4 days. Interestingly, azithromycin, the current recommended treatment[16] was only evaluated in one study.

#### 3.4.2. Carrion's disease

One observational study[14] evaluated both phases of Carrion's disease, but only data for the eruptive phase, verruga peruana, were available. The authors reported the response rate by day 10 of treatment as 'good', 'fair', and 'poor', when the reduction in lesion size and improvement in color was ≥90%, 50–90%, and <50%, respectively. The study compared the use of rifampin vs. streptomycin; there was no statistically significant difference in the achievement of a good response (OR 0.30, 95% CI 0.07–1.37, $p = 0.12$).

#### 3.4.3. Chronic bacteremia

Using the pooled data from two studies (one RCT and one observational study), the use of gentamicin and doxycycline showed a statistically significant increase in the resolution rate of chronic bacteremia compared with no treatment (OR 15.90, 95% CI 2.68–94.53, $p = 0.02$, $I^2 = 0$) (Figure 3). An RCT showed an increase in the time to achieve cure compared to no treatment (reported only in one RCT; WMD 8.50 days, 95% CI 2.76–14.24, $p = 0.004$).

#### 3.4.4. Bacillary angiomatosis

One of the observational studies evaluated bacillary angiomatosis[30] in patients with HIV. The study did not show a statistically significant difference between the use of erythromycin and doxycycline in terms of cure rate (OR 6.50, 95% CI 0.28–151.123, $p = 0.24$) or relapse rate (OR 1.96, 95% CI 0.08–48.26, $p = 0.68$). Compared with amoxicillin–clavulanate, cefuroxime, or imipenem, erythromycin showed a statistically significant difference in

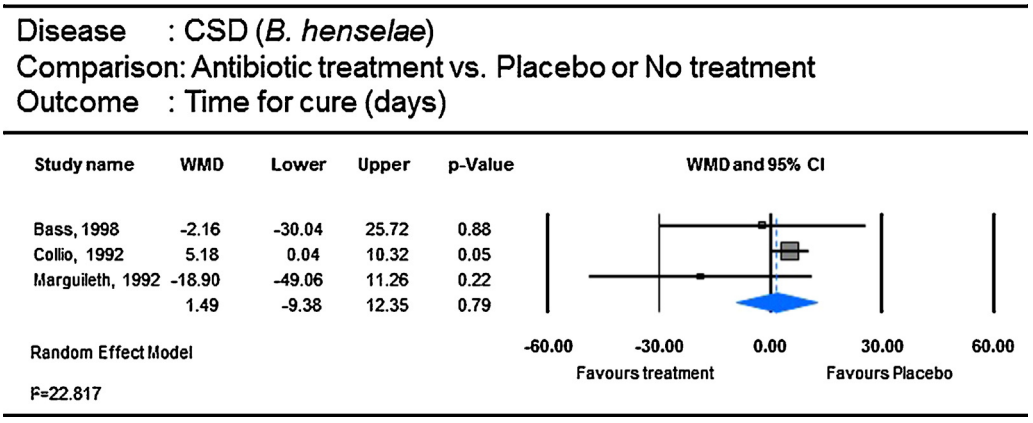


**Figure 2.** Forrest plot: Cat scratch disease.

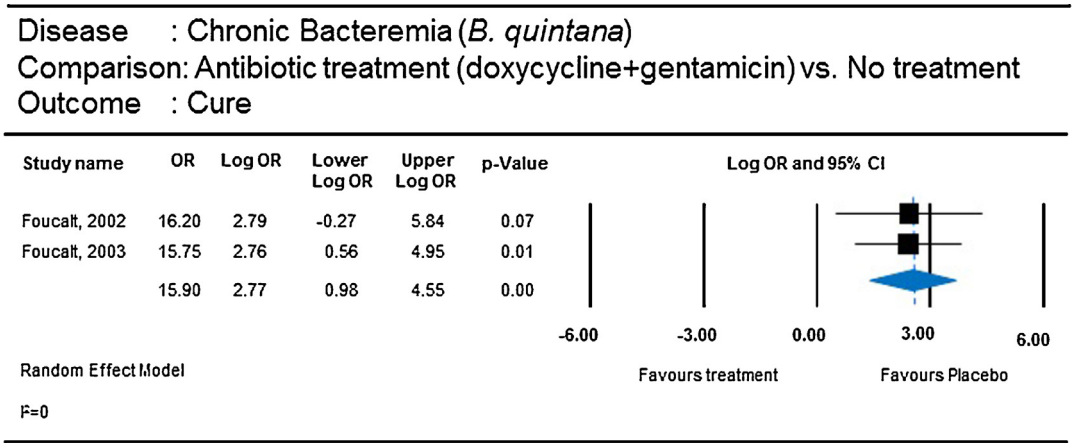


**Figure 3.** Forrest plot: Chronic bacteremia.

**Table 4**
Quality assessment

Randomized controlled trials

| Study | Blinding | Randomization method | Allocation concealment | Lost to follow-up | Base-line imbalances | Efficacy follow-up | Adherence follow-up | Source of funding |
|---|---|---|---|---|---|---|---|---|
| Bass 1998 | Care givers, patients | Table of random numbers | NR | 17.14% | No | All study subjects were reevaluated clinically and by repeat ultrasonography studies | The administration of several doses was supervised | NR |
| Foucault 2003 | Open label | Prepared blocks of envelopes | No | 20% | No | Patients in the treatment group were hospitalized for the first 14 days for treatment. For the remaining 14 days patients received their treatment either in the hospital or in medical facilities | Patients in the treatment arm were hospitalized and untreated controls were monitored either in the hospital or in medical facilities of the city shelters | NFP |

Observational studies

| Study | Selection | | | Comparability | Outcome | | | Source of funding |
|---|---|---|---|---|---|---|---|---|
| | Representative of exposed, selection of the non-exposed | Ascertainment of exposure | Outcome was not present at the beginning | Comparability of cohorts | Similar assessment | Was follow-up long enough? | Non-response rate | |
| Arisoy 1999 | Patients treated in a tertiary care center. All the participants came from the same center | Yes | Yes | Same community and same management | Yes, quite similar | Yes | 0% | NR |
| Collio 1992 | Patients with mild disease. All the participants came from the same center | Yes | Yes | Same community and same management | Yes, quite similar | Yes | 0% | NR |
| Foucault 2002 | Homeless people. All the participants came from the same center | Yes | Yes | Same community and same management | Yes, quite similar | Not clear | 14% | NFP |
| Margileth 2002 | Unclear | NR | Yes | Same community and same management | Yes, quite similar | Not clear | 0% | NR |
| Maguina 2001 | Patients of both genders, wide range of ages. All the participants came from the same center | Yes | Yes | Same community and same management | Yes, quite similar | Yes | 0% | NR |
| Plettenberg 2000 | HIV patients. All the participants came from the community | Yes | Yes | Same community and same management | Yes, quite similar | Yes | 0% | NR |
| Raoult 2003 | Patients with high risk factors. All the participants came from the same community | Yes | Yes | Same community and same management | Yes, quite similar | Not clear | 0% | NR |

NFP, not for profit; NR, not reported.

cure rate (OR 37.8, 95% CI 1.45–980.75, $p = 0.03$), but not in relapse rate (OR 0.06, 95% CI 0.002–1.31, $p = 0.07$); doxycycline did not show a statistically significant difference in cure rate (OR 7.00, 95% CI 1.168–291.34, $p = 0.306$) or relapse rate (OR 0.029, 95% CI 0.000–1.99, $p = 0.1$) when compared with the same treatments.

We did not find any studies meeting our criteria that evaluated patients with peliosis hepatis.

#### 3.4.5. Infectious endocarditis

Infectious endocarditis caused by *B. henselae* or *B. quintana* was reported in one observational study.[31] The recommended treatment for this disease includes gentamicin and ceftriaxone with or without doxycycline;[16] hence we considered aminoglycoside + β-lactams as the intervention of interest. This combination was not statistically more effective than other antibiotic treatment (β-lactams alone, such as amoxicillin, ceftriaxone, benzylpenicillin, and oxacillin; rifampin ± other, aminoglycosides ± other, doxycycline ± other non-aminoglycoside, and fluoroquinolones ± other) in cure rate (OR 1.55, 95% CI 0.66–3.63, $p = 0.31$), death rate (OR 0.78, 95% CI 0.33–1.86, $p = 0.58$), or relapse rate (OR 0.20, 95% CI 0.01–3.74, $p = 0.58$).

## 4. Discussion

We conducted a systematic review and meta-analyses to determine the efficacy of different antibiotic regimens in the treatment of infection caused by the three most common species of human Bartonella (*B. henselae*, *B. quintana*, and *B. bacilliformis*).

### 4.1. Main findings

#### 4.1.1. Cat scratch disease

The available data do not support the use of antibiotics for the management of CSD. No particular antibiotic regimen was shown to be beneficial in improving the cure rate or time to achieve cure. Therefore, the unknown benefit with the potential for adverse effects limits the recommendation of a preferred approach.

Considering the severity of the potential sequelae of the systemic disease (hepatosplenic disease, neuroretinitis, neurologic disease), it is quite concerning that that there is no available evidence for treatment efficacy, safety, or prevention of disease. It remains unclear whether the antibiotic treatment of a localized disease reduces the risk of the development of a systemic disease. Well designed and conducted RCTs evaluating the benefits and harms of azithromycin, currently recommended as the therapy of choice, are needed.[16]

#### 4.1.2. Carrion's disease

The disease is characterized by an initial febrile or hematic phase known as Oroya fever; if untreated it may have a mortality risk higher than 40%.[8] Currently the recommended treatment includes chloramphenicol or ciprofloxacin.[16] Considering the high mortality risk, the lack of evidence to support any of these treatments is concerning.

For the second (eruptive) phase of the disease, also known as verruga peruana, the recommended treatment is rifampin or streptomycin, and our meta-analysis showed that there is no difference between them. However, the evidence to support their benefits over other therapies, even in guidelines, is weak[16] and sometimes contradictory with microbiological research.[32]

#### 4.1.3. Chronic bacteremia

The meta-analysis demonstrated that the treatment of patients with chronic bacteremia (caused by *B. henselae* and/or *B. quintana*) with gentamicin and doxycycline, in accordance with the current recommendation,[16] increases the cure rate. However, the treatment effect was only evaluated by a negative blood culture and not by clinical symptomatology, clinical deterioration, and development of endocarditis or mortality. Having evidence measuring the impact on these clinically important outcomes would be more important from a patient point of view and provide a rationale for the current recommendations.

#### 4.1.4. Bacillary angiomatosis

The only study that involved immunocompromised patients included in this review evaluated bacillary angiomatosis in HIV patients. The study showed that erythromycin might be better than other antibiotics, but with no statistically significant difference from doxycycline.

#### 4.1.5. Infectious endocarditis

The incidence of this complication is low; however endocarditis caused by these pathogens can lead to significant morbidity due to large valvular vegetations and embolic phenomena requiring valve replacement.[33] The need for antibiotics in this presentation is clear, but the current recommended regimen (gentamicin and ceftriaxone with or without doxycycline[16]) was not better than other combinations.

In general, the available evidence for all the evaluated syndromes and antibiotic combinations is of low quality due to the high risk of bias and imprecision (Figure 3).

### 4.2. Limitations and strengths

The quality of the evidence presented in this review is very low due to the small number of studies, low quality, high rates of loss to follow-up in the RCTs, heterogeneity, and imprecision (small sample size and wide confidence intervals).

The strength of this review relates to the comprehensive nature of the literature search and the inclusion of 10 non-indexed journals, increasing the sensitivity of the search strategy. We also followed several measures to reduce the effect of bias such as establishing a predefined protocol, duplicate study selection, and attempting to contact the authors of the included studies.

Although there is no standardized method for the diagnosis of these diseases most of the included studies used microbiological evidence for the diagnosis of the infection. We consider this the ideal method for the diagnosis of an infection caused by *Bartonella spp*.

### 4.3. Implications for practice

In some of the Bartonella syndromes known to have a high mortality, or in complications such as bacillary angiomatosis, infectious endocarditis, or Oroya fever, antibiotic treatment should be provided empirically. The comparative effectiveness evidence is insufficient to allow the favoring of one of these regimens over another. In other Bartonella syndromes such as CSD, withholding antibiotics should be evaluated on an individual basis since evidence of benefit that exceeds adverse effects is unavailable.

## 5. Conclusions

This review demonstrates that the current clinical practice for the treatment of immunocompetent and immunosuppressed patients with Bartonella infections relies mostly on personal experience, expert opinion, and microbiological susceptibility data. Randomized trials are needed in the field to compare different treatment options.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2013.02.016.

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